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EXAMINER	
KASTURI, SRIRAM	

ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/594,990	WORCEL, MANUEL	
	Examiner	Art Unit	
	SRIRAM KASTURI	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 September 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1-29-07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Objection: In claims 6 and 11 the word 'hypertension' is spelled as 'hypterension' needs correction.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating sickle cell anemia or thalassemia in a patient, doesn't reasonably provide enablement for a blood disorder in general. For example leukemia is a blood disorder, but is not enabled. Similarly other blood disorders like Sepsis, HIV/AIDS, Filariasis etc are not enabled. The specification does not enable any person skilled in the art to which it pertains, or with which it most nearly connected, to make and/or use the invention commensurate in the scope with this claim.

To be enabling, the specification of the patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557, 1561 (Fed. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. PPG v. Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996).[1]

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth by In re Wands, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing Ex parte Forman, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,
2) the amount of direction or guidance provided,
3) the presence or absence of working examples,
4) the nature of the invention,
5) the state of the prior art,
6) the relative skill of those in the art,
7) the predictability of the art, and
8) the breadth of the claims.

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. In re Fisher, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the Wands factors are relevant to the instant fact situation for the following

reasons:

1. The nature of the invention, state and predictability of the art, and relative skill level

The invention relates to methods of treating "blood disorders" in general with nitric oxide donor compounds. The relative skill of those in the art is high, that of an MD or PHD. That factor is outweighed, however, by the unpredictable nature of the art. As illustrative of the state of the art, the examiner cites Michalevicz (US 5,104,653), which teaches use of interferons to regulate the in vitro differentiation of multilineage lympho-myeloid stem cells circulating in hairy cell leukemia (HCL) Interferons regulate the in vitro differentiation of multilineage lympho-myeloid stem cells in hairy cell leukemia (Col.2, lines 14-17). Accordingly, it is clear that nitric oxide donors would not be expected to be effective against this particular "blood disorder". Similar reasoning applies to various other blood disorders, e.g. HIV, whose treatment would not reasonably be expected to correlate in a substantial manner to nitric oxide modulation.

2. The breadth of the claims

The claim is very broadly drawn to methods for treating "blood disorders" with nitric oxide donors, as previously discussed.

3. The amount of direction or guidance provided and the presence or absence of working examples

[1] As pointed out by the court in In re Angstadt, 537 F.2d 498 at 504 (CCPA 1976), the key word is "undue", not "experimentation".

The specification provides no direction or guidance for practicing the claimed invention in its "full scope". No reasonably specific guidance is provided concerning useful therapeutic protocols for treating blood disorders other than sickle cell anemia or thalassemia.

4. The quantity of experimentation necessary

Because of the known unpredictability of the art, and in the absence of experimental evidence, no one skilled in the art would accept the assertion that the instantly claimed agents could be predictably used to treat blood disorder in general as inferred by the claim and contemplated by the specification. Accordingly, the instant claims do not comply with the enablement requirement of §112, since to practice the claimed invention in its "full scope" a person of ordinary skill in the art would have to engage in undue experimentation, with no assurance of success.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

1. Claims 2-5, 7-10, 12-15, 17-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 2, 7, 12 and 17 recite "therapeutic agents" without specifying what the agents are effective for.

2. Claims 1-20 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. Specifically, claims 1-10, 11-15, 16-20 fail to provide a subject for the verb "administering", i.e. the claims are incomplete insofar as they do not say to whom or what the combination is administered.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

1. Claims 1 and 2 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pinsky et al (US 6,316,403 B1).

Applicant is claiming treating sickle cell anemia or thalassemia with nitric oxide donor (Claim 1) and further comprising an antioxidant and/or one therapeutic agent (Claim 2).

Pinsky et al teach treating different ischemic disorders including sickle cell anemia (Col.11, lines 10-11), using a composition comprising P-selectin antagonist and a nitric oxide (NO) precursor such as L-arginine, an NO donor such as nitroglycerin or nitroprusside (Col.10, lines 60-63). Their teachings include use of thrombolytic agent tissue plasminogen activator (TPA), i.e., an additional "therapeutic agent" as required by instant claim 2 (Col. 92, Claim12)

The specific combination of features claimed is disclosed within the broad generic ranges taught by Pinsky et al, but such "picking and choosing" within several variables does not necessarily give rise to anticipation. Corning Glass Works v. Sumitomo Elec., 868 F.2d 1251, 1262 (Fed. Circ. 1989). Where, as here, the reference does not provide any motivation to select this specific combination of variables, anticipation cannot be found.

That being said, however, it must be remembered that "[w]hen a patent simply arranges old elements with each performing the same function it had been known to perform and yields no more than one would expect from such an arrangement, the combination is obvious". KSR v. Teleflex, 127 S,Ct. 1727, 1740 (2007)(quoting Sakraida v. A.G. Pro, 425 U.S. 273, 282 (1976)). "[W]hen the question is whether a

patent claiming the combination of elements of prior art is obvious", the relevant question is "whether the improvement is more than the predictable use of prior art elements according to their established functions." (Id.). Addressing the issue of obviousness, the Supreme Court noted that the analysis under 35 USC 103 "need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." KSR v. Teleflex, 127 S.Ct. 1727, 1741 (2007). The Court emphasized that "[a] person of ordinary skill is... a person of ordinary creativity, not an automaton." Id. at 1742.

Consistent with this reasoning, it would have been obvious to have selected various combinations of various disclosed ingredients from within a prior art disclosure, to arrive compositions "yielding no more than one would expect from such an arrangement".

Thus picking sickle cell anemia from ischemic disorders and choosing NO donor nitroglycerin or nitroprusside for treating sickle cell anemia in combination with a therapeutic agent, tissue plasminogen activator (TPA) would have been obvious.

2. Claims 3-5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pinsky et al (US 6,316,403 B1) in view of Loscalzo et al (WO 02/34303 A1).

Pinsky et al teach methods for treating an ischemic disorder including sickle cell anemia using a composition comprising P-selectin antagonist and an NO donor such as nitroglycerin or nitroprusside and TPA as described above. Their teachings lack nitric

oxide donor N-hydroxy-L-arginine, isosorbide dinitrate and an antioxidant hydralazine compound.

Loscalzo et al teach methods of treating vascular diseases due to nitric oxide insufficiency also disclose use of a antioxidant hydralazine compound and isosorbide mono-or dinitrate that donate, transfer release or stimulate endogenous NO synthesis (Abstract). Their teachings include use of N-hydroxy-L-arginine as a compound that stimulates endogenous NO or elevate levels of endogenous endothelium-derived relaxing factor (EDRF) in vivo and is a substrate for the enzyme, nitric oxide synthase (Page 27, lines 2-5). Their preferred antioxidant is hydralazine hydrochloride, which is also a preferred pharmaceutically acceptable salt (Page 22, lines 29-31).

It would have been obvious to one of ordinary skill in the art to use therapeutically effective amount of NO donor, N-hydroxy-L-arginine and antioxidant hydralazine hydrochloride as a therapeutic agent in Pinsky et al's pharmaceutical composition, since N-hydroxy-L-arginine is an NO donor with many advantages as taught by Loscalzo et al and it is desirable to have an antioxidant in a pharmaceutical composition to minimize loss due to oxidation of individual components.

3. Claims 6-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pinsky et al (US 6,316,403 B1) in view of Loscalzo et al (WO 02/34303 A1).

Pinsky et al teach methods for treating an ischemic disorder sickle cell anemia using a composition comprising P-selectin antagonist and an NO donor such as nitroglycerin or nitroprusside and TPA as described above. Thus sickle cell anemia a

blood disorder is an NO dependent disease.Their teachings lack pulmonary hypertension and an antioxidant.

Loscalzo et al teach methods of treating vascular diseases due to nitric oxide insufficiency with their composition containing NO donor, N-hydroxy-L-arginine and antioxidant hydralazine hydrochloride as described above. Loscalzo et al teachings include pulmonary hypertension and cardiac ischemia as vascular diseases characterized by NO insufficiency (Page 14, lines 15- 20).

It would have been obvious to one of ordinary skill in the art to use therapeutically effective amount of NO donor N-hydroxy-L-arginine and antioxidant hydralazine hydrochloride as a therapeutic agent in Pinsky et al composition with additional advantages as taught by Loscalzo et al to treat pulmonary hypertension in a patient with sickle cell anemia.

4. Claims 11-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Loscalzo et al (WO 02/34303 A1) in view of Pinsky et al (US 6,316,403 B1) and Bandaru et al (US Pub No. 2003/0064439 A1) in combination.

Loscalzo et al teach methods of treating vascular diseases due to nitric oxide insufficiency with their composition containing NO donor, N-hydroxy-L-arginine and antioxidant hydralazine hydrochloride as described above. Loscalzo et al teachings include pulmonary hypertension and cardiac ischemia as vascular diseases characterized by NO insufficiency (Page 14, lines 15- 20). Their teachings lack thalassemia.

Pinsky et al teach methods for treating sickle cell anemia using a composition comprising P-selectin antagonist and an NO donor such as nitroglycerin or nitroprusside and TPA as described above. Thus sickle cell anemia is an NO dependent disease.Their teachings lack thalassemia which is another red blood cell disease.

Bandaru et al while teaching isolated nucleic acid molecules that encode novel polypeptides also disclose disorders involving red cells including sickle cell disease and thalassemia (Page 109 paragraph 1195, lines 1-5).

It would have been obvious to one of ordinary skill in the art to use a composition comprising N-hydroxy-L-arginine an NO donor and antioxidant hydralazine hydrochloride to treat pulmonary hypertension in a patient with thalassemia as taught by Loscalzo et al. Since both thalassemia and sickle cell anemia are red blood cell diseases as taught by Bandaru et al, and sickle cell anemia is an NO dependent red blood cell disease as taught by Pinsky et al.

5. Claims 16-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pinsky et al (US 6,316,403 B1) in view of Loscalzo et al (WO 02/34303 A1).

Pinsky et al teach methods for treating sickle cell anemia using a composition comprising P-selectin antagonist and an NO donor such as nitroglycerin or nitroprusside and TPA as described above. Thus sickle cell anemia is an NO dependent disease. Their teachings lack oxidative stress and an antioxidant.

Loscalzo et al teach methods of treating vascular diseases due to nitric oxide insufficiency with their composition containing NO donor, N-hydroxy-L-arginine and antioxidant hydralazine hydrochloride as described above. Loscalzo et al teach vascular diseases characterized by NO insufficiency including oxidative stress. (Page 14, lines 15-16).

It would have been obvious to one of ordinary skill in the art to use therapeutically effective amount of NO donor N-hydroxy-L-arginine and antioxidant hydralazine hydrochloride as a therapeutic agent in Pinsky et al composition with additional advantages as taught by Loscalzo et al and antioxidant hydralazine hydrochloride to prevent degradation of components, to treat oxidative stress in a patient with sickle cell anemia.

Conclusion:

Claims 1-20 are rejected. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SRIRAM KASTURI whose telephone number is (571)270-5263. The examiner can normally be reached on Monday-Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick Krass can be reached on 571-272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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